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A study on an immune network dynamical system model

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§1. Introduction

Recently, there has been considerable interest in the development of autonomous networks in various fields. Autonomy in information devices in personal and home network and the research related to ad hoc networks are especially active areas. Immune systems seem to be good examples of autonomous network systems that do not have central management. I have been interested in whether dynamical models of immune systems may give us an understanding of this aspect of immune systems. At this research meeting, I report about the characteristics of immunity seen in some dynamical network models.

First, I give an about the outline of immunity in §2, and then explain the dynamical model in §3. In §4, I describe the relation between the formation process of the network and its structure. A summary and guidelines for the future are mentioned at the end.

§2. Immune system

We humans have two immune systems in our body. One is natural immunity, the other is adaptive immunity. All animals have natural immunity. In this system, phagocytes, complements and cytokines work together. Natural immunity has low recognition and fast action (on the order of minutes or hours). But, it does not change with age or experience of transmission, and it has no memory. Only vertebrate animals also have adaptive immunity. In this system, lymphocytes, antibodies, and cytokines work together. It has high recognition and slow action (on the order of days).

Next, I will explain about the solid structure in the antibody which is the leading part of this research. The typical shape of immunoglobulin is like the letter Y (Fig.1).

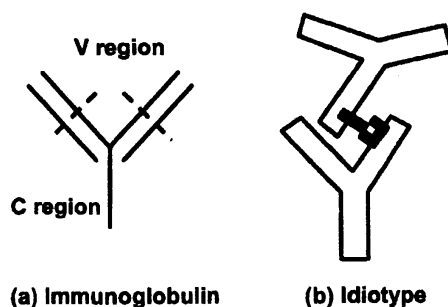


Fig. 1 The basic structure of (a) immunoglobulin, (b) Idiotype

The upper part of the Y is called the “variable region” because the arrangement of the gene often causes mutation and rich changes. In contrast, the part at the bottom of the Y is called the “constant region” (Fig. 1 (a)). We call the three-dimensional structure of the V region, which is characteristic of each immunoglobulin, an idiotypic (Fig.1 (b)).

There are two kinds of immunoglobulin. One is the membrane-bound immunoglobulin. It uses B-cell antigen receptors. B-cells connect antigens with this receptor. And they have the same structure of antibodies, which they can produce. Generally, B-cells cannot produce only through this action. It is a trigger for the setup of antibody generation in B-cells.

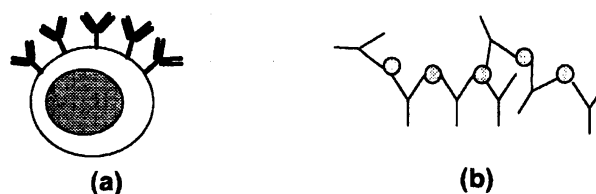


Fig. 2 (a) B-cell and membrane-bound immunoglobulin and (b) antibodies

The other kind is secreted immunoglobulin. Generally, this is called an antibody. Antibodies have several roles in the immune system. First, antibodies neutralize antigens. And antibodies make it easier to reject invading antigens. For example, the C regions of antibodies excite phagocytes, and the antibodies and antigens make a cross-link structure. They become big lumps, and so they are easily found by other immunocytes.

When B-cells are activated, they produce antibodies. There are some roots that exist for B-cell activation. One is the T-cell-independent response. Two typical materials make this type of reaction.

Material objects, which cause cell division, immediately activate B-cells. which cannot recognize the antigen. This is not remembered.

The antigens that have the structure repeated with the same antigenic determinants can cross-link the receptors of B-cells to recognize the antigen. This reaction is also not remembered.

Another is the T-cell-dependent response.

First, the macrophage preys on an antigen. It expresses the protein of the antigen that resolved it in its cell surface, and gives the antigen presentation. The changed phagocyte is recognized by a helper T-cell, and the helper T-cell influences the maturity of the B-cell by using the chemical substance of interleukin. This interleukin is the cause of fever and inflammation. The activated B-cell matures with splitting. Some parts of the split B-cell maintain memory cells, and the other parts become plasma cells. Plasma cells can produce antibodies, and memory cells can change to plasma cells quickly. As a response proceeds,

its suspension is influenced to the B-cell with the use of interleukin by a suppressor T-cell, and the response is settled.

In 1974, Jerne advocated the theory of the idiotypic immune network (ref.1). His theory is as follows.

Generally, an inactive immune system is activated with the invasion of antigens. However, we want to keep minimum number of active immune system members. For this reason, when there is no invasion of antigens, a minimum number of members are activated with the personal protein and the cell. For example, an antibody molecule is formed inside the body due to an unintentional mutation. The new antibody formed at random must be a foreign substance for the antibody that has existed inside the body from the first. Because of that, we can easily imagine that an antibody to react with the antibody is newly formed. In this way, one antibody responds to another antibody as an internal image of external antigens and we keep a minimum number of active immune system members. This is his theory, the network theory. This theory is partly right and it is experimentally well known that the antibodies of the neogenesis mouse have antibody-antibody interaction. But because the experimental study is very difficult to conduct on adult animals, and because other immune cells, T-cells, etc., and some classes of interleukins have been discovered, the network theory has received less attention.

In 1988, Varela et al. proposed a dynamical system model in which both B-cells and antibodies are taken into account (ref. 2). He introduced the effects of T-cells and interleukin as functions of the B-cell. Here, I introduce some models of theoretical immunology and recent fields of application.

In 1989, Bagley et. al. defined the 3-dimensional structure of antigens, and investigated the topology of the network (ref. 3). In 1990, Parisi investigated the capacity of memory with the simple spin-glass idiotypic network model (ref. 4). In 1993, De Boer et. al. considered the structure of the cross-link of Mlgs, and advocated the B-model (ref. 5). In B-models, B-cells proliferate according to a phenomenological log bell-shaped function. In addition, there is the activated preparation of antigen generation model, the vaccinated model, and so on

§3. Model

In this study, we use Varela's model.

One of the reasons is that there are two equations, for both antibodies and B-cells. And the effects of interleukins and T-cells are described as a function of the maturation and proliferation of B-cells. This model is described by the following two equations (equation 1).

$$\begin{aligned}\frac{df_i}{dt} &= -K_1\sigma_i f_i - K_2 f_i + K_3 \text{Mat}(\sigma_i) b_i \\ \frac{db_i}{dt} &= -K_4 b_i + K_5 \text{Prol}(\sigma_i) b_i + K_6\end{aligned}\quad (1)$$

$i=1,\dots,N$, f_i ; concentration of antibodies, b_i ; concentration of B-cells
 $\text{Mat}(\sigma_i)$; function of maturation of B-cells, $\text{Prol}(\sigma_i)$; function of proliferation of B-cells,
 K_1 ; the rate of death by antibody-antibody interaction, K_2 ; the rate of natural death of
antibodies, K_3 ; the rate of antigens generated by B-cells, K_4 ; the rate of natural death of
B-cells, K_5 ; the rate of increase of B-cells, K_6 ; the rate of supply of B-cells from bone marrow

First, there is the equation of the concentration of antibodies. In this equation, the first term is death by antibody-antibody interaction, the second term is the natural death of antibodies, and the third term is antigen generated by B-cells. Second, there is the equation of the concentration of B-cells. In this equation, the first term is the death of B-cells, the second term is the increase of B-cells division, and the third term is supply of B-cells from bone marrow. This pair of equations describes the behavior of the i th clone. If there are two clones, the concentrations of two clones change in the anti-phase. For example, B-cell 1 can generate free antibody-1. There are many B-cell-1s and produced free antibody-1s. We call the whole group "CLONE".

The constituents of the network, the free antibodies and B-cells, interact with each other through idiotypes. Between two different idiotypes i and j , there may occur an affinity, which is represented by the connectivity m_{ij} . We set $m_{ij} = 1$ if there is an affinity between i and j , and $m_{ij} = 0$ if there is none. In some cases, $m_{ij} = 1$ is experimentally measurable. The sensitivity of the network for the i th idiootype is defined as

$$\sigma_i = \sum_{j=1}^N m_{ij} f_j \quad (2).$$

The probability of the maturation and proliferation of B-cells is assumed to depend on their sensitivity σ . An antibody is formed only from a B cell (plasma cell) that has matured. It is well known that both of these functions have dual thresholds depending on affinity.

In order to understand the effect of the maturation and proliferation functions, we change these functions. Even though the function was changed, we found that typical behaviors were maintained (ref. 6). Because of these results, we modify the model by choosing simpler functions (Fig. 3).

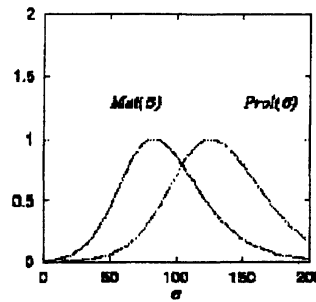


Fig. 3 The mature and proliferation functions used in this study

Here, we introduce a threshold above which antibodies can recognize antibodies and antigens. This is because recognition is not possible if the concentration of antigens inside the body isn't comparatively high. In this case, there are some non-symmetric limit cycles depending on the value of the threshold. We call this condition the differentiating state. Next, we set the elements of a connectivity matrix depending on the concentration of antibodies. If i does not equal j , when $f_i > f_0$, antibody j is recognized by other antibodies, and $m_{ij} = 1$. And when $f_i < f_0$, antibody j is not recognized, and $m_{ij} = 0$. Here, because we assume they don't have self connectivity, if i equals j , $m_{ij} = 0$.

Next, we studied response to the external perturbation in a small network. In a small network of this model, non-symmetric limit cycles exist. In a 3-clone network, each clone has an S-state or L-state condition and there is a differentiating state with two L-state and one S-state clones.

The S-state has a short time over the threshold, and the L-state has a long time over the threshold. Now, clones can respond to an antigen only when their antibody concentration is over the threshold. In view of this, the S-state is unsuitable and the L-state is suitable for reacting with antigens. It can also be said that the short-term memory of the network is suitable when the clone is L-State (ref. 6).

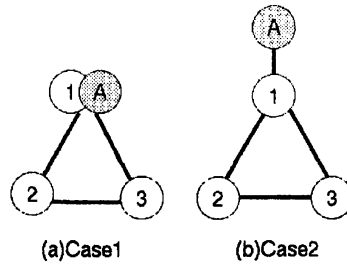


Fig. 4 Antigen invasion

We considered two cases of antigen invasion in a 3-clone system (Fig. 4). In case 1, we consider that external antigens similar to antibodies f_1 invade the 3-clone closed network. In case 2, we consider that external antigens interact only with clone-1. In both cases, we introduce the antigen equation as follows.

$$\frac{dA}{dt} = -K_1 \sigma_A(t) A + K_7 \quad (3)$$

A is the concentration and K_7 is the increase rate of antigens. And in this equation, σ_A is defined respectively in case 1 (4) and case 2 (5).

$$\sigma_A(t) = m_{12}(t)f_2(t) + m_{13}(t)f_3(t) \quad (4)$$

$$\sigma_A(t) = \Theta(f_1(t) - g_{1,0})f_1(t) \quad (5)$$

In both case 1 and case 2, when the reproduction rate of antigens becomes high, it shifts to a more proper attractor arrangement, and the antigens are caught.

We also study antigen invasion in a 4-clone system in 3 cases, (a) the case where a clone that can respond with antigens is L-State, (b) the case where a clone that cannot respond with antigens is L-State, and (c) the case where the system is chaotic. In this figure, we compared the average time of antigen moderation.

The relaxation time T_a for case (a) is the shortest, and T_b for case (b) is the longest. Relaxation time T_c for case (c) is between T_a and T_b . These results suggest that a chaotic state is more effective than the differentiating states for preparing for various types of

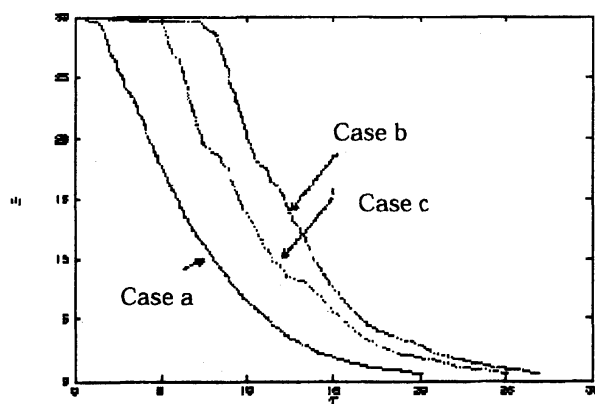


Fig. 5 (a) The clone that can respond with antigen A is L-state, (b) the clone that can NOT respond with antigen A is L-state, (c) the system is chaotic

We have written in detail about these results in ref. 6.

§4. Formation process and network structure

Before considering a large network, it is an important problem to consider whether a network is truly one network or whether it can be divided into sub-networks. If the network can be divided into sub-networks, the study of the smaller networks is very important. As for this model, the condition that the concentration of each clone's antibody and the B cell oscillates is called "activation".

We analyze the activated conditions of a large network for the case in which each clone interacts with all other clones or only a few other clones in the network (ref. 7). When each clone interacted with all clones in the network, we did not find any activated clone in the network. Furthermore, when each clone interacted with only a few other clones, we found that many clones are activated in the network. Therefore, in this model, each clone must have only a few other connections to activate the network.

We also studied the effect of threshold as a localized mechanism of immune response (ref. 8). The roles of the threshold in units are as follows. When it is attacked by antibodies, a network with a threshold doesn't break easily from a network without a threshold. By introducing a threshold, the independence of each clone is increased, the collapse of the network is made more difficult, and the size of the parameter areas where the system functions as a network increases.

To check the role of the threshold in the network, we connect three basic units loosely (Fig.

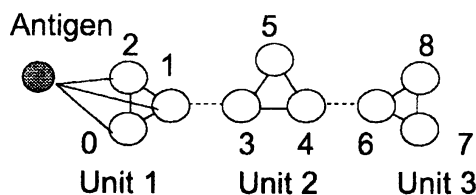


Fig. 6 Connection of 3-clone units

There is no threshold in each basic unit. We set the threshold between each unit, to $k_u=0$ or $k_u=50$. We examined the way that of fluctuation spreads when unit 1 was disturbed. In both cases, the disturbance does not spread significantly to unit 3. Further, we have found that the disturbance in unit 2 is reduced considerably for $k_u=50$, while it is still large for $k_u=0$. As a result, the threshold prevents the spread of local fluctuation through the whole network (Fig. 4).

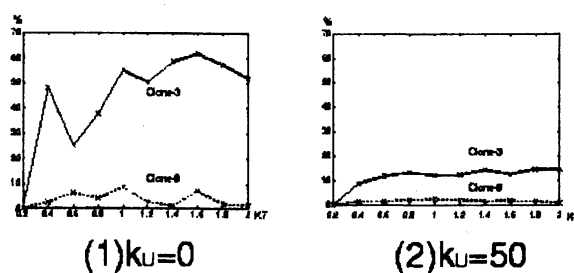


Fig. 7 K7 dependence of the magnitude of fluctuation s in clones 2 and 8 relative to that in clone 0

As for the actual reaction of immunity, it is very important that antibody molecules cross-link for phagocyte prey antigens. In real immune systems as well, it is feasible that a concentration threshold exists in some way.

Next, I will explain the relation between the generation process and the structure of the network.

What kind of difference is there in the structure of the network through the different formation processes? How does the network divide into sub-networks? I want to know what kind of difference occurs in the structure of the network through the different formation processes.

In the network in which we introduced a threshold, we can measure the time over the threshold. These times are characteristic depending on the condition of each clone. For example, when we investigate the running average of this time, if the clone is L-state, the time T_L is about 45, if the clone is S-state, the time T_S is about 22. If the clone has a limit

cycle, this time is about constant. So, I investigate the running average of the time over the threshold.

First, I define the values of connectivity keeping the characters of a small network. When I connect ten 3-clone systems loosely, each clone wanders about around the S-state and the L-state. At that time, the group that has many connections is the motive power in the network. I also found that responses to the invasion of antigens to each unit have characteristics in common with the small network case. The sub-network structure and the threshold are also important for preventing the spread of a local fluctuation throughout the whole network. I think that if a large network can be divided into small sub-networks, the study of the small networks is important. For this reason, I study what type of mechanism I can introduce into this model to make a sub-network structure.

First, I define the values of connection at random. If the number of nodes in the network is small enough, there are some cases where networks have sub-networks. However, when the network size becomes large enough, there are no sub-networks.

So, I introduce a newer phenomenon. This is the phenomenon of affinity maturation (ref. 9). Because of the substitution of amino-acid due to mutation, the affinity of the antibody changes. B cells cause mutation frequently in the process of the immune response. There is a possibility that the new antibody has more or less sensitivity than the parent antibody. The state of activation of these B-cells changes corresponding to the concentration of the antigens. When the network has a high concentration of antigens, both sensitive and insensitive antigens are activated. Also, when the network has a low concentration of antigens, only sensitive antibodies are activated. Therefore, as the immunity reaction proceeds, the affinity of the antigens is sensitive. I imitate this phenomenon, and change the value of the connectivity corresponding to the amount of time it is over the threshold.

I define values of connectivity constantly at random in a 30-clone system, and change them in accordance with a condition. Here, I change the values of connectivity depending on the number of times over the threshold. Then, some limit cycles appear, but there are no sub-networks.

Next, I will introduce the mutation mechanism in the model.

B-cells cause mutation frequently in the process of the immune response. So we introduce meta-dynamics - not the whole network generated at once, but the growth of the network by mutation (Fig. 5). A clone exceeding a threshold affects the mutation of other B-cells. However, the new kind of clone generated due to the mutation does not always have a good response to the antibodies that led to that mutation. The initial condition of the network is two different 3-clone systems. Here, 1, 2, 3, 4 or 5 clones become new members of the network in every unit time. The occurrence probability of how many clones come to the

network is 20% each. Various network structures are seen depending on the generation rules.

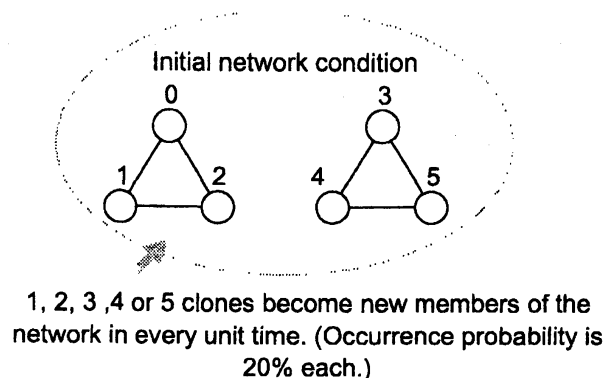


Fig. 8 Initial network condition and mechanism of mutation model

As one case, I define the value of connectivity between the new members generated due to mutation and the existing member, which caused the mutation. These values are decided at random in accordance with the following ratios: the proportion of 0.0 is 20%, 0.02 is 20% and 1.0 is 50%. The values of connectivity between new members are decided at random in accordance with the following ratios: the proportion of 0.0 is 30%, 0.02 is 30% and 1.0 is 40%

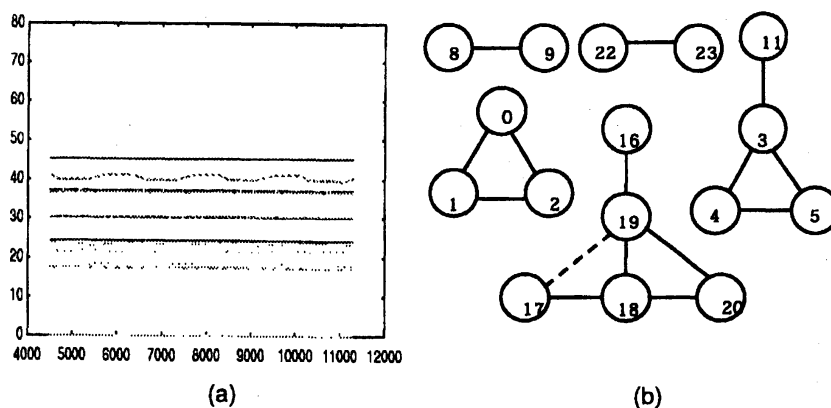


Fig. 9 One case of a network configuration of a mutation model

When a network grows gradually by a mechanism that imitates mutation, we can show that some sub-networks are generated. Possibly, the mutation mechanism may be the cause of the sub-network structure being made.

§5. Summary

First, at least in a small network, it is found that the idiotypic network model proposed by F. J. Varela can appropriately work for external perturbation.

Second, in the case of some clones connected at random, if the number of clones in the network is large, we cannot see any sub-networks, because the system behavior is chaotic. In the case of some clones connected at random, if the values of connectivity are changed in accordance with some assumptions, some limit cycle states may appear.

Fourth, a network has various structures which are dependent on the formation process. Also possibly, a mutation-like generation mechanism creates the sub-network structure.

In this study, some characteristics of the immune network model have been revealed. In the future I want to examine applications to other fields.

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